U.S. Food and Drug Administration

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Good Clinical Practice (GCP) Roles, Responsibilities and Inspections

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Disclaimer

- This communication constitutes an informal communication that represents the best judgment of the speaker at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

CDER's BioResearch Monitoring ("BiMo") Inspection Program

- Evaluates adherence to applicable regulations with respect to:
  - Good Clinical Practice (GCP)
    - Clinical Investigators
    - Sponsor-Monitors, Contract Research Organizations
    - Institutional Review Boards
  - Good Laboratory Practice (GLP)
    - *In vivo* Bioequivalence

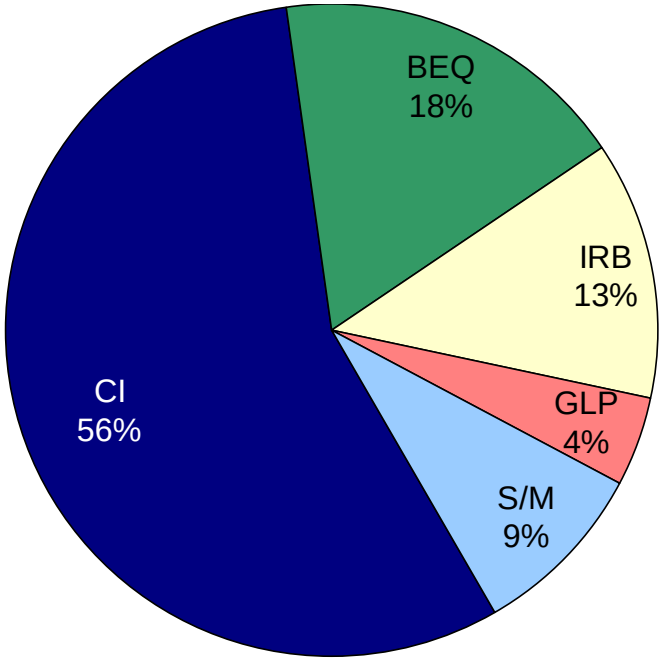
Compliance Program Guidance Manuals (CPGM)

- Provide guidance and instructions to FDA staff conducting inspections
  - 7348.001 In Vivo Bioequivalence
  - 7348.808 Good Laboratory Practice (Nonclinical Laboratories)
  - 7348.809 Institutional Review Board
  - 7348.810 Sponsors, Contract Research Organizations, and Monitors
  - 7348.811 Clinical Investigators

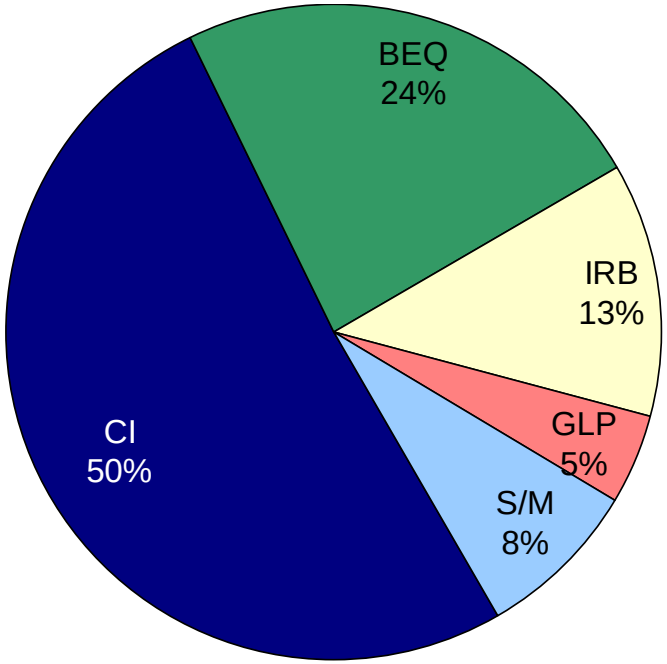
http://www.fda.gov/ICECI/ComplianceManuals/ComplianceProgramManual/default.htm#bimo

Bioresearch Monitoring Program Inspections* (CDER, FY 2009-2010)

FY 2009 (N= 843)



FY 2010 (N= 769)



CI	**=**	**393**
BEQ	**=**	**183**
IRB	**=**	**97**
GLP	**=**	**35**
S/M	**=**	**61**
Total		**769**

*Based on inspection start date
Preliminary data; FY10 subject to change [1/21/2011]

DSI's Role in CDER's GCP Inspections

1. Determine need for inspection
2. Assign and perform inspections through Office of Regulatory Affairs (ORA)
3. Critically evaluate ORA inspectional findings and proposed classification (NAI, VAI, OAI)
4. Make final classification of the inspection
5. Prepare written communication to inspected party
6. Provide a summary of inspectional findings and recommendations to OND Review Division regarding the reliability of data

When Are Inspections Needed?

- For Cause (complaints from any source)
  - To evaluate allegations that raise concerns about data integrity or concerns about compromise of the rights, welfare, and safety of study subjects

- Marketing application related
  - All New Molecular Entities (NMEs)
    - Clinical Investigators
    - Sponsors / CROs
  - NDA/BLA Supplements
    - Inspections not always required
    - Significant expansion of the indication
    - Significant expansion of the patient population
    - Significant safety concern(s)
    - Data integrity issues

Specific Reasons For Inspections (but not limited to…)

Evidence/suspicion of the following

- Misrepresented or unrealistic data
- Rejection of data by the sponsor
- Under-reporting of adverse events
- Inadequate monitoring of clinical investigations
- Significant financial interest in the product by the investigator

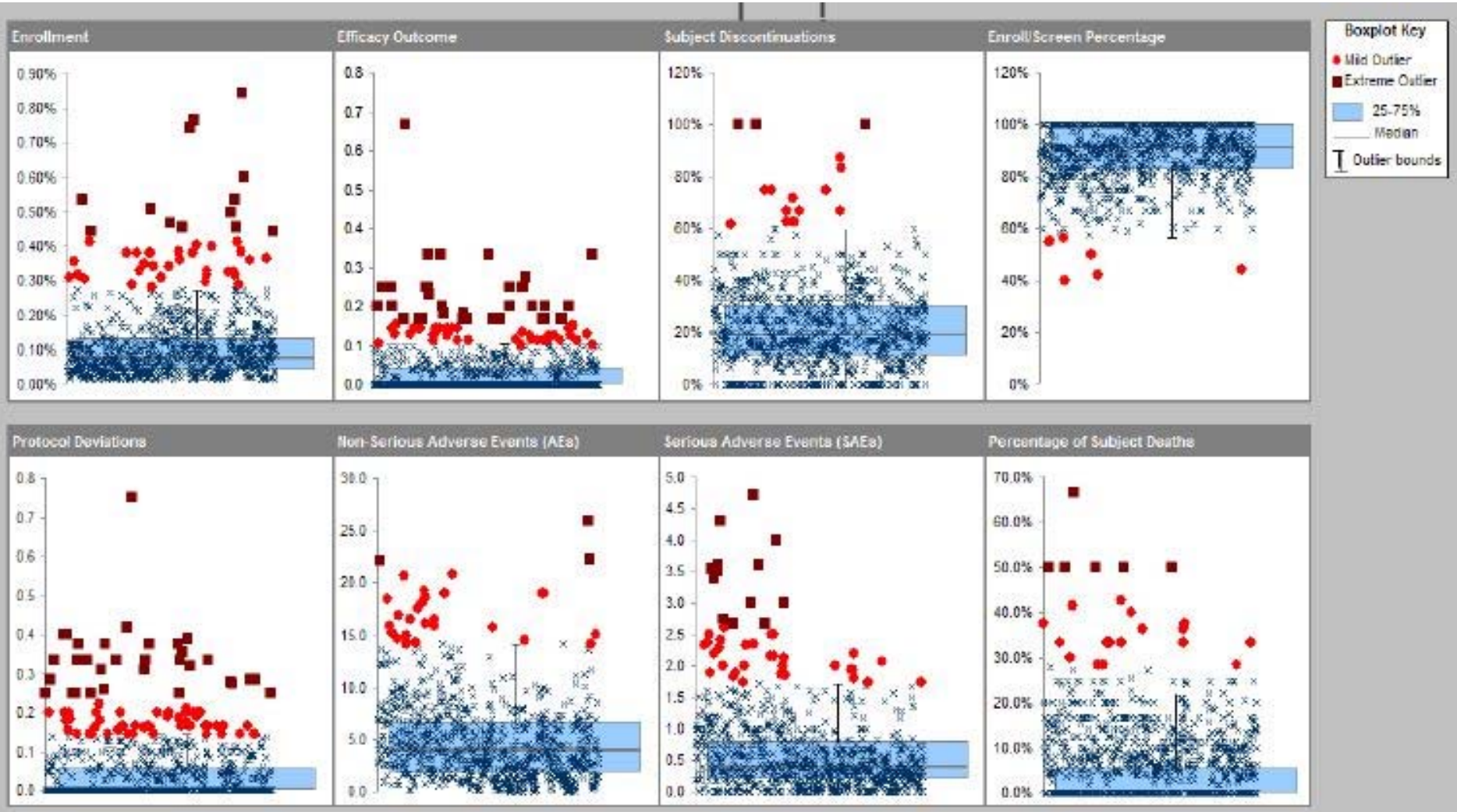
Specific Reasons for Inspections (con't)

- Insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making

Rationale For Clinical Investigator Selection

- A specific safety concern at a particular site or sites
  - Based on review of adverse events (AEs, serious AEs, deaths) or discontinuations
- A specific efficacy concern based on review of site specific efficacy data
  - Efficacy differential between sites
  - Final outcome driven by a particular site or sites
  - Efficacy outcome different than expected based on mechanism of action of drug
- Specific concern for scientific misconduct at one or more sites based on review of
  - financial disclosures,
  - protocol violations,
  - study discontinuations,
  - safety and efficacy results

CDER Risk-based Site Selection Tool Pilot



Inspection Conduct

- DSI assigns and performs inspections through the Office of Regulatory Affairs (ORA)

- DSI reviewers or other subject matter experts from CDER may accompany ORA investigators on inspections on an as needed basis

Post-Inspection Outcome and Evaluation

- ORA investigator may issue a Form FDA 483 at close of inspection, which lists inspectional observations (immediately available via FOI)

- ORA investigators prepares an Establishment Inspection Report (EIR)
  - Includes exhibits supporting all observations including deficiencies
  - Recommends inspection Classification (NAI/VAI/OAI)
  - Submitted to Division of Scientific Investigation for review

Post-Inspection Outcome and Evaluation

1. DSI reviews EIR and pertinent exhibits

2. DSI provides a summary of inspectional findings and recommendations to Office of New Drugs (OND) Review Division regarding the reliability of data generated by inspected entities:
   - Did observed violation affect:
     - Efficacy or safety data?
     - Subject safety, rights, or welfare?
   - Frequency of observed deficiency
   - Source of observed deficiency:
     - Isolated occurrence at CI site?
     - Systemic issue relating to study planning or oversight?

3. DSI makes final classification of the inspection and prepares written communication to inspected party

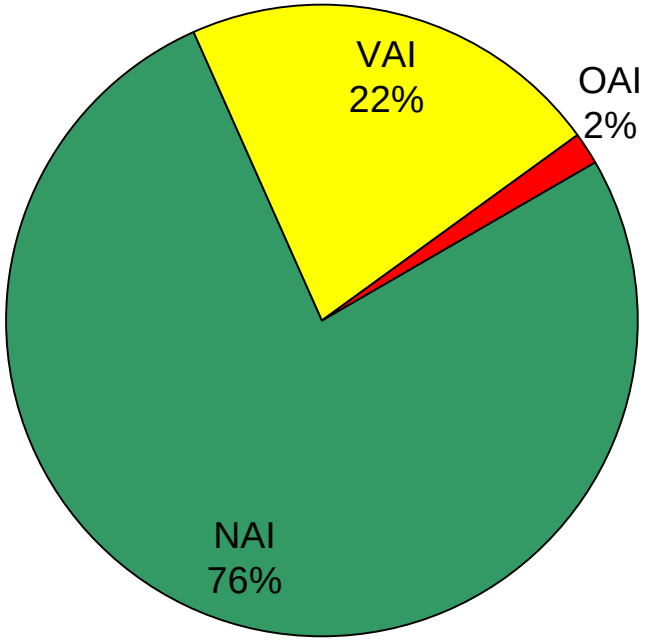
Inspection Outcomes

- **NAI**: No Action Indicated
- **VAI**: Voluntary Action Indicated
- **OAI:** Official Action Indicated

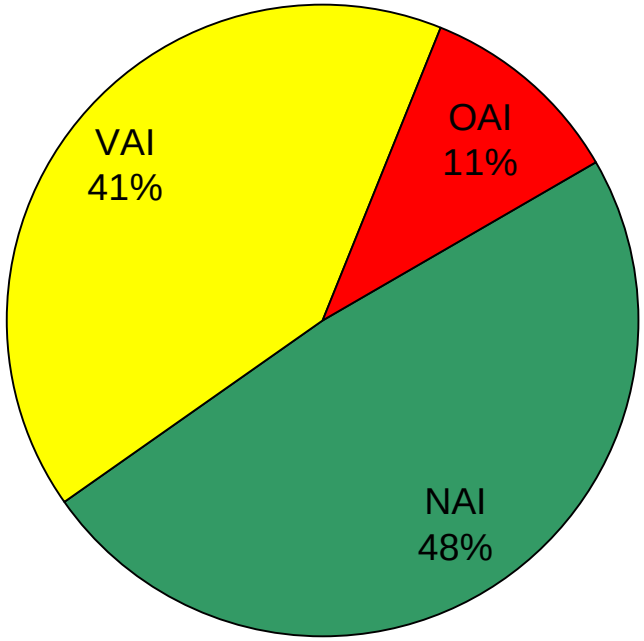
*Based on Letter Issued Date

Example: Sponsor/CRO Inspections Final Classification* (CDER, FY 2009-2010)

FY 2009 (N= 60)



FY 2010 (N= 66)*



*Based on letter issue date; Includes OAI Untitled Letters; Preliminary data; FY10 subject to change [1/21/2011]

Role of Inspection Results

- In aggregate, inform DSI/review decisions about data integrity and approvability for the application as a whole
  - Isolated occurrences at individual clinical sites, effectively addressed?
  - Or systemic issues relating to study planning or oversight?

- Public Health Impact
  - Regulatory Action by FDA/DSI
    - Warning Letters
    - Notice of Initiation of Disqualification Proceedings
    - Disqualification of CI
  - Criminal Investigation by Office of Criminal Investigations (OCI)

Inspection Follow-up

- At the inspection close-out meeting with FDA, use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made
- FDA will consider any written response received within 15 business days of the issuance of a 483 when determining appropriate action
- Recommendations for an effective response:
  - Assess each observation
  - Focus on the regulatory requirement(s) associated with the observation
  - Consider root-cause analysis – are there system-wide and global implications
  - Be specific (e.g. observation-by-observation), complete and realistic
  - Provide time frames for correction
  - Provide method of verification and/or monitoring for corrections

Information Sources

DSI
http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm

List of Disqualified or Restricted Investigators
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

Warning Letters
http://www.fda.gov/foi/warning.htm

NIDPOE Letters
http://www.fda.gov/foi/nidpoe/default.html

Debarment List
http://www.fda.gov/ora/compliance_ref/debar/default.htm

Clinical Investigator Inspection List
http://www.fda.gov/Drugs/InformationOnDrugs/ucm135198.htm